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Yttrium-89 NMR: A Possible Spin Relaxation Probe for Studying Metal Ion Interactions with Organic Ligands

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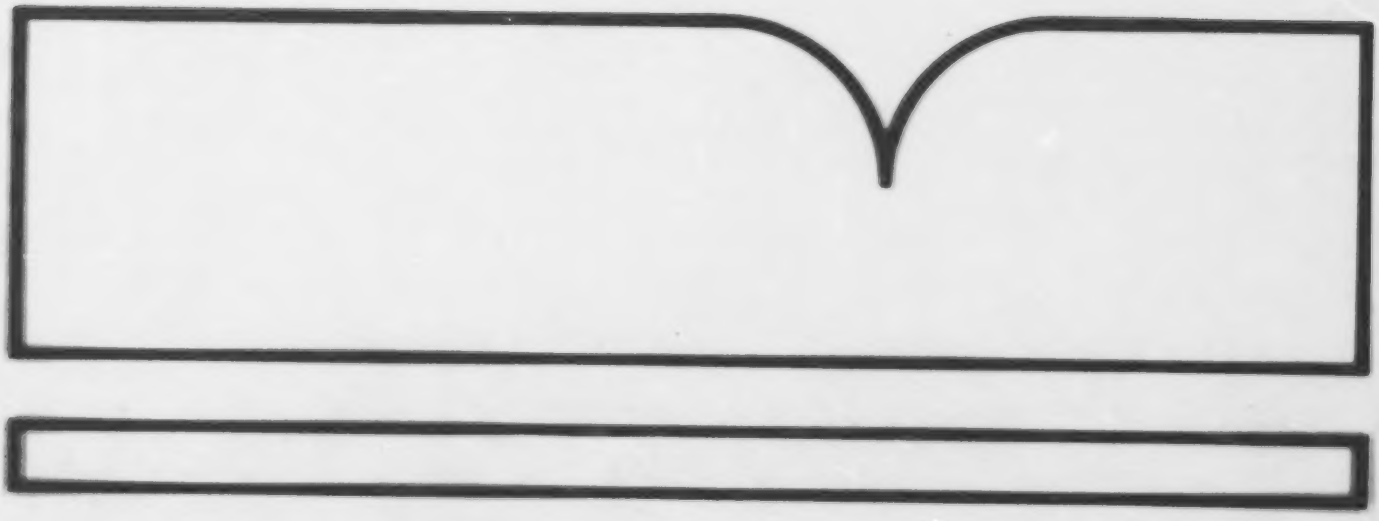

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16. ABSTRACT

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Yttrium-89 NMR. A Possible Spin Relaxation Probe for Studying Metal Ion Interactions with Organic Ligands

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The spin–lattice relaxation mechanisms for aqueous and dimethyl sulfoxide solutions of $Y(NO_3)_3$ have been found to be mainly spin–rotation and dipolar relaxation with solvent protons, unlike most heavy spin $=\frac{1}{2}$ metal ions which are relaxed mainly by spin–rotation and chemical shift anisotropy. The theoretical maximum $^{89}Y\{^1H\}$ NOEF value of -10.2 was observed when τ_c for the ion was lengthened by lowering the temperature of the aqueous salt solution to 5°C, or when yttrium was complexed to an organic ligand. Since ^{89}Y has a sensitivity of 0.67 relative to that of ^{13}C, the relative importance of dipolar relaxation and the large theoretical maximum NOEF make ^{89}Y a possible valuable NOE structure probe. Such studies can complement relaxation and shift data obtained from other diamagnetic and paramagnetic lanthanide ions.

INTRODUCTION

As a consequence of its small and negative magnetic moment (at 3.52 T, 150 MHz for ^1H, ^{89}Y is observed at 7.34 MHz), ^{89}Y is thought to be a difficult nucleus to observe by NMR. Complications result from long T_1's and low sensitivity. Largely for these reasons only three ^{89}Y NMR studies have been reported (*1–3*).

Nevertheless, the nuclear properties of ^{89}Y (100% natural abundance and $I=\frac{1}{2}$) partially offset its low sensitivity, and make this nucleus a potentially useful probe for the study of interactions of organic and biological molecules with metal ions. In addition to the possibility of observing scalar coupling to other $I=\frac{1}{2}$ nuclei such as ^{15}N, ^{31}P, and ^{13}C, large NOEF values are possible when ^{89}Y is relaxed by dipolar interactions with other nuclei. For example, when ^{89}Y is dipolar relaxed by ^1H, a theoretical maximum NOEF $=-10.2$ is possible. Thus assuming largely dipole–dipole relaxation, ^{89}Y–^1H NOE values[1] could be used as a probe for the proton environment in metal complexes.

In theory any $I=\frac{1}{2}$ metal ion is suitable for NOE studies. However, high or moderate γ nuclei such as ^{207}Pb, ^{195}Pt, ^{113}Cd, ^{199}Hg, ^{205}Tl, and ^{119}Sn are not optimal because observed NOEF values are relatively small (2.8 to 0.87). Nuclei such as ^{183}W and ^{57}Fe are undesirable because of their low natural abundance. Furthermore, most

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[1] NOE = NOEF + 1, where NOE is defined as the ratio of integrated intensities of the peak with and without proton irradiation.

spin-$\frac{1}{2}$ metal NMR studies to date show efficient spin–rotation and chemical shift anisotropy relaxation, with reduced levels of dipolar relaxation (*4*). If the lanthanide-like ("electrostatic" bonding) ^{89}Y nucleus undergoes predominantly dipolar relaxation, then $^{89}Y\{^1H\}$ NOE values could be used to probe yttrium binding to large molecules.

EXPERIMENTAL

Yttrium-89 spectra were obtained on the in-house design 3.52-T Seminole (*5*) FT NMR spectrometer operating at 7.349 MHz using 25-mm sample tubes (20 ml of sample). Free-induction decays were measured using 2K data points, quadrature detection, and a ±200-Hz spectral window (90° pulses for ^{89}Y required 90 μsec). Carbon-13 spectra were obtained on a Bruker HX-270 spectrometer at 67.9 MHz using 8K data points, quadrature detection, and a ±1500-Hz window.

Yttrium nitrate hexahydrate 99.9% was obtained from Alfa Chemicals, and used without further purification. Solvents were dimethyl sulfoxide (Burdick and Jackson distilled-in-glass, dried over molecular sieves) and distilled water. The yttrium nitrate/crown ether complexes were prepared by a method used for other rare earth/crown ether complexes (*6*). Elemental analyses (performed by Atlantic Microlab Inc., Atlanta, Ga.) were acceptable and indicated anhydrous complexes of all the crown ether complexes studied.

Values of T_1 were measured using a time-saving FIRFT 180°–τ–90° pulse sequence (*7*), and the data were fitted to an exponential curve obtained from a plot of intensity vs τ using a nonlinear three-parameter fit (*8*). A 1.0 *M* aqueous solution of yttrium perchlorate revealed no significant pH dependence for T_2 (as measured by NMR linewidths, which were $\Delta\nu_{1/2} < 0.3$ Hz and were limited by magnet inhomogeneity) from pH = 0 to 2, as has most recently been reported (*3*). Also, despite the long T_1's no measurable effect of oxygen on T_1 was observed for 1.0 *M* $Y(NO_3)_3$, pH = 0, T = 35°C. Consequently, all other samples were run without degassing. The complete dipolar relaxation observed at lower temperatures is further evidence of the absence of paramagnetic relaxation, consistent with a previous report (*3*). NOEF values ($NOEF_{max} = -10.2$) were determined using gated decoupling (decoupler gated ON during data acquisition and OFF during delays of at least $5T_1$ between pulses, to suppress NOE). Viscosities were measured using Cannon–Manning viscometers in a water bath thermostated to ±0.5°C.

RESULTS AND DISCUSSION

The relaxation data for aqueous $Y(NO_3)_3$ solutions are given in Table 1. At 35°C, in 1.0 *M* solution, approximately 25% of the relaxation is accounted for by dipolar interactions with the solvent, H_2O. This is not surprising since Y^{3+} ions are expected to be highly solvated. The observed T_1 for 1.0 *M* $Y(NO_3)_3$ over a 60°C temperature range is relatively constant. Such a temperature dependence is characteristic of large contributions to T_1 from spin–rotation, which has an inverse temperature depen-

TABLE 1

RELAXATION AND NOEF DATA FOR AQUEOUS $Y(NO_3)_3$ SOLUTIONS

Concentration (M)	T (°C)	η (cP)	T_1[a]	NOEF[b]	T_1^{DD}	T_1^{OTHER}
1.0[c]	5		270	−10	275	1000
	15		240	−6.0	400	600
	25	1.90	180	−4.6	400	300
	35	1.46	240	−2.5	980	300
	65	0.88	130	−0.7	2000	140
3.0	25	15.5	63	−2.6	250	84
	35	12.2	85	−1.8	480	103
	65	4.96	75	−0.9	850	82

[a] ±10–15%.
[b] ±15%, theoretical maximum NOEF = −10.2.
[c] pH = 1.8.

dence compared to the other common relaxation mechanisms:

$$\frac{1}{T_1^{SR}} = \frac{\pi I^2}{3h^2} C_{eff}^2 \frac{1}{\tau_c}, \qquad [1]$$

$$\frac{1}{T_1^{DD}} = \gamma_Y^2 \gamma_H^2 \hbar^2 \frac{1}{r^6} \tau_c. \qquad [2]$$

At lower temperatures where spin–rotation becomes inefficient, relaxation is entirely dipolar, as evidenced by the virtually full NOEF at 5°C:

$$\text{NOEF} = \eta = 0.5 \frac{\gamma_H^1}{\gamma_Y^{89}} \frac{T_1^{Tot}}{T_{1\{^1H\}}^{DD}}. \qquad [3]$$

This high NOEF value also demonstrates the relative unimportance of paramagnetic contributions to the relaxation rate from dissolved oxygen. This is largely due to the γ_Y^2 dependence of $T_1^{PARAMAGNETIC}$, assuming only dipolar paramagnetic relaxation:

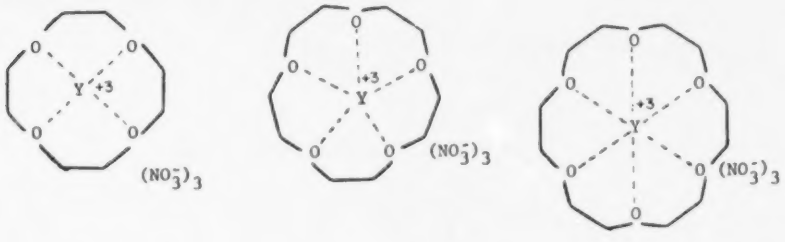
$$\frac{1}{T_1^P} = \tfrac{1}{15}\gamma_Y^2 \gamma_e^2 h^2 S(S+1) \frac{6}{1+\omega_Y^2 \tau_C^2} + \frac{14}{1+\omega_S^2 \tau_C^2} \frac{1}{r^6} \tau_c. \qquad [4]$$

The T_1's obtained from 1.0 M $Y(NO_3)_3$ are significantly longer than the 60- to 80-sec T_1 reported for 3.0 M $Y(NO_3)_3$ (*3*). These results were confirmed in our laboratory (Table 1). This effect is not explained as a result of more efficient dipolar relaxation in the more viscous solution. Although T_1^{DD}'s in 3.0 M solution are shorter than T_1^{DD}'s in 1.0 M solution, contrary to expectations, NOEF values are smaller in the more concentrated solutions. Also, in the more concentrated solutions, the residual T_1^{OTHER} is relatively constant over a broad temperature range, indicating a balance between T_1^{SR} and some other mechanism.

In order to understand this concentration dependence of T_1, it must be remembered that $Y(NO_3)_3$ is likely to contain other lanthanides (most of those necessarily

are paramagnetic) as impurities. At triple the concentration, and at higher viscosity, relaxation contributions may become important from these lanthanides acting as nonspecific dipolar relaxation reagents. Additional small contributions from other mechanisms such as dipolar relaxation from inner sphere $^{14}NO_3^-$, paramagnetic relaxation from dissolved oxygen, or chemical shift anisotropy cannot be ruled out in the 3 *M* solution.

From the temperature dependence of T_1^{DD} reorientational activation energies (E_a) of 26 and 25 kJ/mol were calculated from the 3.0 and 1.0 *M* solutions, respectively. These values may seem high compared to a value of 10.5 kJ/mole obtained for ion relaxation of $^{85}Rb^+$ and $^{23}Na^+$ (*9*). However, when the charge-to-radius ratio of Y^{3+} and Na^+ (which have similar ionic radii) is considered, this high activation energy is not surprising.



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With the hope of slowing molecular motion, in order to eliminate spin–rotation contributions to relaxation, and also to provide an additional nucleus to observe, crown ether complexes of yttrium were examined. These results are presented in Table 2. For reasons of solubility, these compounds were studied in DMSO solution.

TABLE 2

RELAXATION AND NOEF DATA FOR 0.5 *M* Y COMPOUNDS IN DMSO SOLUTION

Compound	*T* (°C)	η (*cP*)	T_1[a]	NOEF[b]	T_1^{DD}	T_1^{OTHER}
$Y(NO_3)_3 \cdot 6H_2O$	35	6.2	260	−5.9	450	620
[c]	35	6.4	550	−2.8	2000	760
1	35	6.3[d]	300	−11	300	
1	65		560	−8.0	714	2600
1[c]	35	7.6	800	−2.0	4000	1000
2	35		400	−5.1	800	800
3	35		330	−6.0	560	800

[a] ±10–15%.

[b] ±15%.

[c] Solvent was DMSO-d_6. As a result of the long T_1 there is a large uncertainty in the accuracy of this T_1 (+50–25%), since a $\tau_\infty > 2T_1$ could not be used (due to hardware limitations of our computer).

[d] $\eta_{35°C} = 1.8$ cP for 0.5 *M* **4** in DMSO.

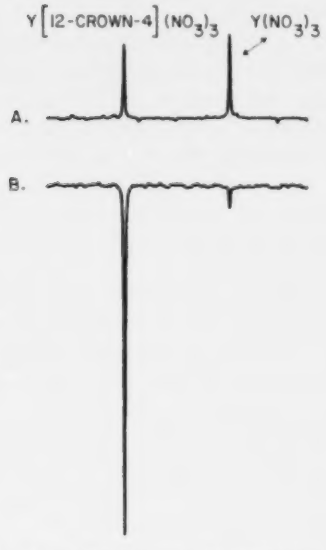

FIG. 1. Yttrium-89 spectrum without NOE (A), and with NOE (B) of 0.5 *M* **1** in DMSO contained in a 25-mm tube, and 3 *M* $Y(NO_3)_3$ in H_2O contained in an internal 10-mm tube (1500-sec delay between pulses, 500-Hz window). In this sample ^{89}Y shows NOEF values of ca. −1.2 and −6 for the aqueous and DMSO solutions, respectively.

For comparison, $Y(NO)_3$ was also studied in DMSO solution. As predicted for a solution of higher viscosity, dipolar relaxation plays a more important role in the relaxation rate of $Y(NO_3)_3$, as a result of longer correlation times. Also, the dipolar relaxation time in deuterated solvent is only four times that obtained in protio-DMSO. Assuming no specific interactions with the solvent or water present, on the basis of proton concentrations, the dipolar contributions from water and DMSO protons should be 8 and 92%, respectively. Thus, even in polar DMSO, yttrium appears for the most part to maintain its hydration sphere.

When **1** is examined at 35°C (Table 2), NOEFs are full, and relaxation is entirely dipolar. The crown ether effectively binds Y^{3+} and eliminates spin–rotation contributions to T_1. This is graphically illustrated in Fig. 1. The high-field peak is 3.0 *M* aqueous $Y(NO_3)_3$ in a concentric 10-mm tube, and the downfield peak corresponds to 0.5 *M* **1** in DMSO. Full dipolar relaxation again demonstrates the unimportance of paramagnetic relaxation from dissolved oxygen, and also the unimportance of chemical shift anisotropy contributions to the relaxation rate of ^{89}Y in **2**.

For **2**, a rapid equilibrium exists in solution between bound and unbound metal ions. As the temperature is increased the relative contribution of spin–rotation from the unbound metal increases, causing a measurable reduction in the NOE. Simultaneously, at the higher temperature, the efficiency of dipolar relaxation in the metal/crown complex becomes less efficient. When DMSO-d_6 is substituted as the solvent T_1^{DD} values of **1** become extremely large. This suggests that the major role of

the crown/ether is to restrict the motion of the cation, but that a major portion of dipolar relaxation still comes from dipolar interactions with solvent molecules, both for uncomplexed Y^{3+} and for the chelated metal ion. The data indicate that dipolar interactions with the ligand protons play a relatively minor role (which is not easily quantified, since the dissociation behavior of the complex is not known). This result is consistent with literature indications that Y^{+3}–DMSO complexes are stable (*10*).

The effect of binding Y^{3+} to 12-crown-4 (**4**) is also noticeable in the ^{13}C relaxation properties of **1** and **4**, where ^{13}C T_1 values were measured as 0.87 and 1.74, respectively (NOEF = 2.0 in both compounds); this is also reflected in the solution viscosities (Table 2).

From the ^{13}C relaxation data obtained for **1**, a value of 3×10^{-11} sec can be calculated for τ_c of the complex. This is in good agreement with the value of 4.0×10^{-11} sec calculated using the Stokes–Einstein relation (*11*), assuming a hard-sphere radius of 4.0 Å, measured from molecular models and using a micro-viscosity correction factor.

The study of ^{89}Y relaxation properties was extended to higher homologous crown ether complexes. These results are also presented in Table 2. The relaxation properties of **2** and **3** are those expected if yttrium were largely uncomplexed. Note that T_1^{OTHER}, which is dominated by spin–rotation, is similar for **2**, **3**, and $Y(NO_3)_3$ solutions. Dipolar contributions to the relaxation rate occur as a result of the general presence of solvent protons with a minor contribution from dipolar interactions to ligand protons in **2** and **3**. These results are consistent with the ^{89}Y chemical shift as a function of the yttrium/crown ether ratio. Compound **4** caused a progressive downfield shift of the ^{89}Y resonance (as a function of added **4**), which amounted to 1.5 ppm for a 1 : 1 ratio of **4**: $Y(NO_3)_3$. Crown ethers **5** and **6** caused no discernible shift in the ^{89}Y resonance. At first, this result is somewhat surprising, since from the diameter of the Y^{3+} ion (1.76 Å) compared with the cavity sizes of the various crown ethers (Table 3), complex **2** is expected to be the most long-lived. However, factors other than cavity size may be responsible for stability. A stable 1 : 1 complex of Ag^+ (ionic diameter of 2.54 Å) with a substituted 15-crown-5 ether has been isolated (*15*).

Dipolar relaxation is a very important contributor to the T_1 relaxation of ^{89}Y. Therefore, the very large NOEF can be extremely useful for signal enhancement. However, as a consequence of its negative magnetic moment, signal nulling can be a

TABLE 3

CAVITY DIAMETERS OF SOME CROWN ETHERS

Compound	Cavity diameter (Å)[a]
12-Crown-4 **4**	1.2–1.5
15-Crown-5 **5**	1.7–2.2
18-Crown-6 **6**	2.6–3.2
21-Crown-7 **7**	3.4–4.3

[a] From Ref. (*10*).

problem, particularly for unassociated ions in protic solvents, where the dipolar contribution to the relaxation rate of ^{89}Y can be small (0 to 20%).

The results from **1** demonstrate possible utility of selective $^{89}Y\{^1H\}$ NOE experiments in providing detailed information about metal binding sites in larger molecules, when exchange lifetimes are too long to use paramagnetic lanthanides as spin probes (*13*). As a result of the low γ for ^{89}Y, NOEFs can be observed for molecules with $\tau_c = 10^{-9}$ sec (at 3.5 T), by contrast with ^{13}C NMR, for example, where NOEF values become quite small for $\tau_c = 10^{-9}$ sec at the same field. For ^{89}Y bound to a molecule with τ_c near 1×10^{-9} sec, dipolar relaxation from a *single* proton (at distance 2.5 Å) is calculated to be 60 sec. Since there are typically many protons in the vicinity of a bound metal ion significantly shorter T_1's can be expected, thus alleviating the problems associated with long T_1's.

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REFERENCES

1. E. Brun, J. Oeser, H. H. Staub, and C. G. Telschow, *Phys. Rev.* **76,** 1528 (1949).
2. C. Hassler, J. Kronenbitter, and A. Schwenk, *Z. Phys. A* **280,** 117 (1977).
3. R. M. Adam, G. V. Fazakerley, and D. G. Reid, *J. Magn. Reson.* **33,** 655 (1979).
4. R. K. Harris and B. E. Mann, "NMR and the Periodic Table," Academic Press, London, 1978.
5. G. C. Levy, R. C. Rosanske, and D. Wright, 19th Experimental NMR Conference, Blacksburg, Va., 1978.
6. J. C. G. Bunzli, D. Wessner, and H. T. T. Oanh, *Inorg. Chim. Acta* **32,** 133 (1979).
7. D. Canet, G. C. Levy, and I. R. Peat, *J. Magn. Reson.* **18,** 199 (1975).
8. J. Kowalewski, G. C. Levy, L. F. Johnson, and L. Palmer, *J. Magn. Reson.* **26,** 533 (1977).
9. M. Eisenstadt and H. L. Friedman, *J. Chem. Phys.* **144,** 1407 (1966).
10. S. Ramalingam and S. Soundarajan, *J. Inorg. Nucl. Chem.* **29,** 1763 (1967).
11. A. Abragam, "The Principles of Nuclear Magnetism," Chap. VIII, Oxford Univ. Press (Clarendon), London, 1961.
12. C. J. Pedersen, *J. Am. Chem. Soc.* **92,** 386 (1970).
13. R. A. Dwek, "Nuclear Magnetic Resonance in Biochemistry," p. 75, Oxford Univ. Press (Clarendon), London, 1975.